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REVIEW

Importance of histological evaluation in endoscopic resection of early colorectal cancer

Naohisa Yoshida, Yuji Naito, Nobuaki Yagi, Akio Yanagisawa

Naohisa Yoshida, Yuji Naito, Nobuaki Yagi, Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan
Akio Yanagisawa, Department of Surgical Pathology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan
Author contributions: Yoshida N, Naito Y and Yagi N designed the research; Yoshida N, Naito Y and Yagi N performed the endoscopic research; Yanagisawa A performed the histopathological research; Yoshida N contributed new reagents/analytic tools and analyzed the data; and Yoshida N wrote the paper. Naito Y was the mentor for this study.
Correspondence to: Naohisa Yoshida, MD, PhD, Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. naohisa@koto.kpu-m.ac.jp
Telephone: +81-75-2515519 Fax: +81-75-2510710
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Abstract

The diagnostic criteria for colonic intraepithelial tumors vary from country to country. While intramucosal adenocarcinoma is recognized in Japan, in Western countries adenocarcinoma is diagnosed only if the tumor invades to the submucosa and accesses the muscularis mucosae. However, endoscopic therapy, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is used worldwide to treat adenoma and early colorectal cancer. Precise histopathological evaluation is important for the curativeness of these therapies as inappropriate endoscopic therapy causes local recurrence of the tumor that may develop into fatal metastasis. Therefore, colorectal ESD and EMR are not indicated for cancers with massive submucosal invasion. However, diagnosis of cancer with massive submucosal invasion by endoscopy is limited, even when magnifying endoscopy for pit pattern and narrow band imaging and flexible spectral imaging color of enhancement are performed. Therefore, occasional cancers with massive submucosal invasion will be treated by ESD and EMR. Precise histopathological evaluation of these lesions should be performed in order to determine the necessity of additional therapy, including surgical resection.

Key words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Early colorectal cancer; Histopathology

Peer reviewers: Dr. Marco Bustamante, Department of Gastroenterology, La Fe University Hospital, Avda. Gaspar Aguilar, 90, 46017 Valencia, Spain; Dr. I Michael Leitman, Chief of General Surgery, Department of Surgery, Albert Einstein College of Medicine-Beth Israel Medical Center, 10 Union Square East, 2M, New York, NY 10003, United States

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INTRODUCTION

The diagnostic criteria for colonic epithelial tumors vary from country to country. In Japan, intraepithelial tumors that display malignant cytological or architectural features are diagnosed as intramucosal adenocarcinoma according to Japanese Classification of Colorectal Carcinoma[1]. On the other hand, in western countries, including England and America, intramucosal epithelial tumors are diagnosed only as dysplasia and adenocarcinoma is diagnosed only if the tumor invades to submucosa be-

yond the muscularis mucosae[2,3]. One reason for this is that intramucosal epithelial tumors are clinically benign and do not metastasize to the lung, liver or lymph nodes. In this review, we compare the criteria for diagnosis of colorectal intraepithelial tumors in Japan and in Western countries and also describe the World Health Organization (WHO) classification and Vienna classification of these tumors[4,5].

Despite these differences in diagnostic criteria, endoscopic therapy, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of adenoma and early colorectal cancer, is performed worldwide[6,7]. Precise histopathological evaluation of these lesions is important for the long-term success of these therapies, as inappropriate endoscopic therapy causes local recurrence of the tumor that may develop into fatal metastasis. We describe the use and therapeutic limitations of EMR and ESD and also show the importance of detailed histopathological evaluation of specimens resected by EMR and ESD. Moreover, we reveal the proper endoscopic method for obtaining appropriate specimens for histopathological evaluation by EMR and ESD.

DIFFERENCES IN THE HISTOPATHOLOGICAL DIAGNOSIS OF COLORECTAL EPITHELIAL TUMORS BETWEEN JAPAN AND WESTERN COUNTRIES

The diagnostic criteria for colonic epithelial tumors vary from country to country. In Japan, the terms "low-grade adenoma," "high-grade adenoma" and "intramucosal adenocarcinoma" are used to describe intraepithelial tumors based on their degrees of cytological or architectural atypia, according to the Japanese colorectal cancer criteria (Table 1)[1]. Intramucosal adenocarcinoma is characterized by malignant glandular epithelium exhibiting a tubular or papillary architecture or producing mucus. In contrast, in Western countries, including England and America, intraepithelial tumors are diagnosed only as dysplasia[2,3] and the term "adenocarcinoma" is used only if the tumor invades the submucosa and accesses the muscularis mucosae. In detail, "mild dysplasia," "moderate dysplasia" and "severe dysplasia" are used in England to classify intraepithelial tumors according to the states of their nuclei, glandular patterns and interglandular spaces (Table 1)[2]. Mild dysplasia and moderate dysplasia are almost similar to the Japanese definitions of low-grade and high-grade adenoma, and severe dysplasia is almost identical to the Japanese definition of adenocarcinoma. In America, "low-grade adenoma" and "high-grade adenoma" are used to describe intraepithelial tumors according to the states of their crypts and nuclei (Table 1)[3]. Low-grade adenoma is almost similar to the English categories of mild and moderate dysplasia, while high-grade adenoma is almost similar to the English category of severe dysplasia. However, the WHO classification, which was revised in 2010, defines dysplasia as histopathologically unequivocal neoplastic epithelium without evidence of invasive growth[4]. The term "dysplasia" is thus only appropriate when cytological and/or architectural features of neoplasia are present. The term "intramucosal adenocarcinoma" is applied to lesions that show histological evidence of invasion into the lamina propria or muscularis mucosa but not into the submucosa.

Table 1 The differences in the histopathological diagnosis of colorectal intraepithelial tumors between Japan and Western countries

	Intramucosal epithelial tumor		
Japan	Low grade adenoma	High grade adenoma	Intramucosal adenocarcinoma
United Kingdom	Mild dysplasia	Moderate dysplasia	Severe dysplasia
United States	Low grade dysplasia		High grade dysplasia

The Vienna classification of gastrointestinal epithelial neoplasia is represented as resolving the histopathological diagnostic differences among other countries[5] and applies to the diagnosis of both biopsy specimens and resected specimens. Epithelial neoplastic lesions are classified as Categories 1 through 5. The detailed criteria are as follows: Category 1, negative for neoplasia/dysplasia; Category 2, indefinite for neoplasia/dysplasia; Category 3, non-invasive low-grade neoplasia; Category 4, non-invasive high-grade neoplasia; and Category 5, invasive neoplasia, including intramucosal carcinoma and submucosal carcinoma or beyond. The revised Vienna classification of gastrointestinal epithelial neoplasia was reported in 2002[8]. This revised classification includes the intramucosal carcinoma in category 4 instead of category 5, which fits better with the possibility of endoscopic therapy of this subtype of carcinoma. However, this Vienna classification system is seldom used clinically in Japan.

The diagnostic criteria for submucosally invasive cancer also vary among countries. As submucosally invasive cancer has a risk of metastasizing, it is generally treated by surgical resection worldwide. However, the risk of metastasis is reported to be about 10%[9]. In Japan, the depth of submucosal invasion is measured as part of the evaluation of submucosally invasive cancer because it affects the risk of metastasis to the lymph nodes[1] (Figure 1). The depth of submucosal invasion is calculated as follows. When the muscularis mucosae can be identified, it is used as the baseline and the vertical distance from this line to the deepest extent of invasion represents the submucosal depth (Figure 2). When the muscularis mucosae cannot be identified due to carcinomatous invasion, the most superficial aspect of the submucosally invasive cancer is used as the baseline and the vertical distance from this line to the deepest portion is determined and defined as the depth of submucosal invasion (Figure 3)[9,10]. The Japanese guide-

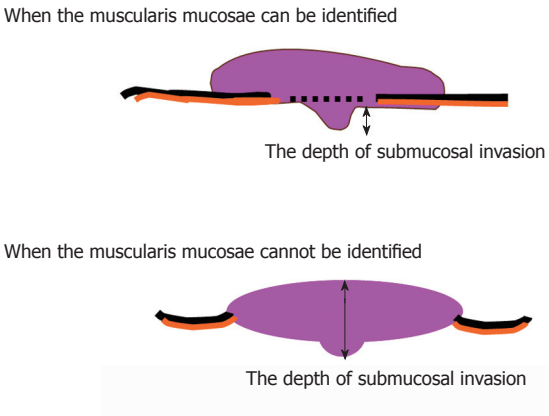

Figure 1 The Japanese system for measuring the depth of submucosal invasion in submucosally invasive cancer. When the muscularis mucosae can be identified, it is used as the baseline and the vertical distance from this line to the deepest extent of invasion represents the depth of submucosal invasion. When the muscularis mucosae cannot be identified due to carcinomatous invasion, the most superficial aspect of the submucosally invasive cancer is used as the baseline and the vertical distance from this line to the deepest extent of invasion is the depth of submucosal invasion.

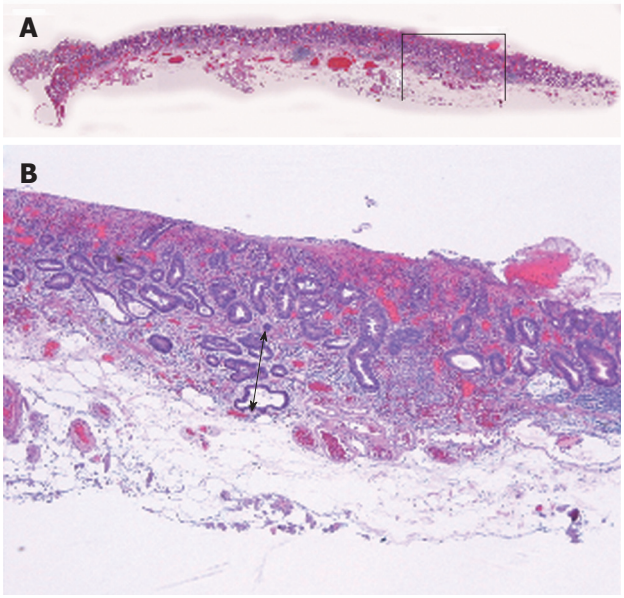

Figure 2 A submucosally invasive cancer with identifiable muscularis mucosae. A: Submucosal invasion (black box) with partial destruction of the muscularis mucosae was detected by histological examination of hematoxylin and eosin stained sections; B: The muscularis mucosae was identified. The depth of submucosal invasion was 500 μm (black arrow).

lines for colorectal cancer report the following risk factors for lymph node metastasis of submucosally invasive colorectal cancer: (1) depth of submucosal invasion more than 1000 μm; (2) lymphatic or venous invasion; (3) poorly differentiated histology; (4) the vertical margin of the resected specimen positive for cancer; and (5) grade 2 or 3 tumor cell budding[10,11]. Evaluation of these risk factors determines whether endoscopically resected submucosally invasive cancer is further treated by surgical resection. In Japan, submucosally invasive cancer in surgically resected specimens is also classified clinically as SM1, SM2 or SM3 according to the degree of invasion into the submucosa[12].

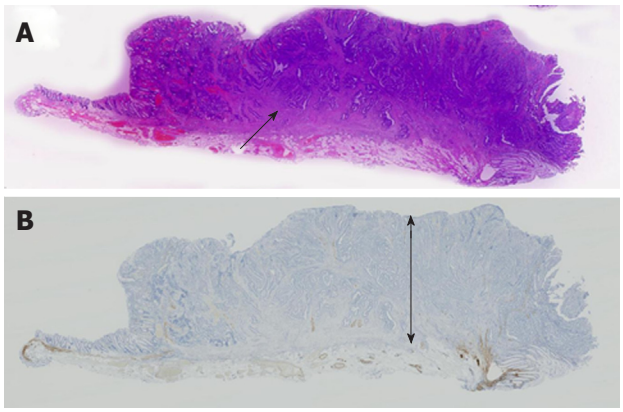

Figure 3 A submucosally invasive cancer with unidentifiable muscularis mucosae. A: Submucosal invasion (black arrow) with complete destruction of the muscularis mucosae was detected by histological examination of hematoxylin and eosin stained sections; B: Immunohistological staining for desmin showed that the muscularis mucosae could not be identified. The depth of submucosal invasion was 3500 μm (black arrow).

The phrase "massive submucosal invaded cancer," which is frequently used in clinical reports, is synonymous with tumor invasion of SM2 or SM3 or with depth of submucosal invasion of more than 1000 μm[9,13-14]. For pedunculated submucosally invasive cancer that has disrupted the muscularis mucosae, the depth of submucosal invasion is the distance between the deepest extent of the invasion and a reference line defined as the boundary between the tumor head and the pedicle, according to Haggitt's classification[15]. When the cancer does not invade past the reference line, it is defined as "head invasion" and has no possibility of metastasis. When cancer has invaded above this baseline, it is defined as "stalk invasion" and additional surgery should be considered to reduce the risk of lymph node metastasis.

INDICATIONS FOR AND THERAPEUTIC LIMITATIONS AND HISTOPATHOLOGICAL EVALUATION OF EMR AND PIECEMEAL EMR

EMR is generally performed for early colorectal cancers worldwide. The saline injection-assisted method was first described by Rosenberg, who identified it as a safety factor for the removal of rectal and sigmoid polyps, and was reintroduced by Tada *et al*[16-18] in 1984. Most adenomas and intramucosal cancers can be resected by EMR; however, tumors greater than 20 mm in diameter are considered difficult candidates for *en bloc* resection[19-24]. The rates of *en bloc* and complete resection have been reported to be 62.85% and 58.66%, respectively[6]. The rate of *en bloc* resection by EMR of tumors greater than 20 mm in diameter is especially insufficient (Table 2)[19-24]. Many additional injection solutions have been used to achieve sustained mucosal elevation, definitive *en bloc* resection and prevention of perforation during EMR. Hypertonic saline, glycerol, dextrose and fibrinogen in-

Table 2 The rates of *en bloc* resection and local recurrence of tumors larger than 20 mm in diameter treated by endoscopic mucosal resection

Author	Injection solution	No. of cases	Rate of *en bloc* resection (%)	Rate of local recurrence (%)
Saito *et al*[18]		228	33.0	14
Tanaka *et al*[19]	Glycerol	178	39.3	7.9
Tajika *et al*[20]		104	48.1	15.4
Iishi *et al*[21]	NS	56	25.0	-
Kobayashi *et al*[22]		56	37.5	21.4
Uraoka *et al*[23]	NS	44	20.5	18.6
	Glycerol	39	23.1	15.2
Our data	HA	35	42.8	10

HA: Hyaluronic acid; NS: Not significant.

Table 3 The rates of *en bloc* resection and complete resection by endoscopic submucosal dissection

Author	No. of cases	Rate of *en bloc* resection (%)	Perforation rate (%)	Post-operative bleeding rate (%)
Saito *et al*[7]	1111	88.0	4.9	1.5
Toyonaga *et al*[32]	468	98.9	1.5	1.5
Isomoto *et al*[33]	292	90.1	8.2	0.7
Yoshida *et al*[34]	250	86.8	6.0	2.4
Fujishiro *et al*[35]	200	91.5	10.4	1.0
Zhou *et al*[36]	74	93.2	8.1	1.3
Tanaka *et al*[37]	70	80.0	10.0	1.4
Our recent data	410	92.6	4.1	1.9

duce longer-lasting mucosal elevation than achieved by normal saline (NS)[24-26]. Uraoka *et al*[24] demonstrated that the rates of *en bloc* and complete resection by EMR were improved by using glycerol rather than NS. Moreover, the increased tumor-free margin achieved using glycerol improved the rate of complete resection. Yamamoto *et al*[27] first reported the efficacy of hyaluronic acid (HA) for novel endoscopic resection of a large colorectal polyp and this procedure was subsequently termed ESD. We also demonstrated that 0.13% HA was effective for achieving sustained mucosal elevation in resected porcine colon and in living minipig colon. HA has been shown to produce higher and more sustainable mucosal elevation than achieved by NS[28]. However, some authors have raised concerns about the theoretical carcinogenetic risk of HA[29]. This should be confirmed by further studies.

Evaluation of *en bloc* resection is performed endoscopically, while complete resection is defined histopathologically based on the tumor-free lateral and vertical margins of the resected specimens. Although specimens resected by EMR sometimes show positive margins even if the tumor was successfully resected *en bloc*, most of such tumors cause no local recurrence. Burning of the resected specimens probably affects this situation. However, some of these tumors recur locally. Therefore, endoscopists are obligated to perform EMR with tumor-free margins. In our department, we have adopted HA as our injection liquid in order to improve our rate of complete resection, especially of large tumors (Table 2).

When *en bloc* resection of the tumor by EMR fails, piecemeal EMR is generally performed instead. Although piecemeal EMR enables the removal of large colorectal tumors, it has a high rate of local recurrence (7.9%-21.4%) (Table 2). Most recurrent adenomas, including partial intramucosal adenocarcinomas, can be cured by additional endoscopic therapy[30]. If possible, the indications for the use of piecemeal EMR should be examined carefully before endoscopic therapy by magnifying endoscopy and image-enhanced endoscopy[31,32]. However, piecemeal EMR does not allow for precise histopathological evaluation in some cases; for example, partial submucosal invasion in submucosally invasive cancer can be missed in piecemeal-resected specimens. When the locus of submucosal invasion in submucosally invasive cancer is destroyed by burning, the tumor may be misdiagnosed as mucosal cancer, and when the positive vertical margin of submucosal or lymphatic-venous invasion is burned, the resection may misclassified as complete. In these cases, the patient will not be advised to undergo additional surgical resection, allowing recurrence a few years later[30]. In some cases, recurrence may occur as lung, liver and/or lymph node metastasis and these patients are very difficult to cure. Therefore, laparoscopic-assisted colectomy (LAC) is regarded throughout the world as the standard therapy for large colorectal tumors[33]. However, as LAC is more invasive than endoscopic treatment, ESD is still performed in some areas, especially in Japan.

INDICATIONS FOR AND THERAPEUTIC LIMITATIONS AND COMPLICATIONS OF ESD

In Japan and some other Asian as well as Western countries, ESD is reported to be an efficient treatment with a high rate of *en bloc* resection for large colorectal tumors and it is less invasive than LAC[7,34-39]. ESD allows removal of large early colorectal cancer lesions but can be a time-consuming procedure and carries a risk of perforation higher than that of EMR[36,40-41]. A list of situations in which ESD is appropriate has been proposed by a Japanese ESD specialist group[39]. These are, firstly, lesions more than 20 mm in diameter for which endoscopic therapy are indicated but for which *en bloc* resection by snare EMR would be difficult and, secondly, lesions that are suspected to be submucosally invasive, which should be resected *en bloc* by ESD. Other lesions in addition to these categories can also be candidates for ESD, including mucosal lesions with fibrosis caused by prolapse due to biopsy or peristalsis, local residual early cancer after endoscopic resection, and sporadic localized tumors in cases of chronic inflammation such as ulcerative colitis. The rate of *en bloc* resection for large colorectal tumors has been reported to be 80.0%-98.9% (Table 3)[7,34-39]. However, the procedure has not been standardized due to its associated technical difficulties. The colon is winding in nature and has many folds. Moreover, the colonic wall is thinner than the gastric wall. The main complications

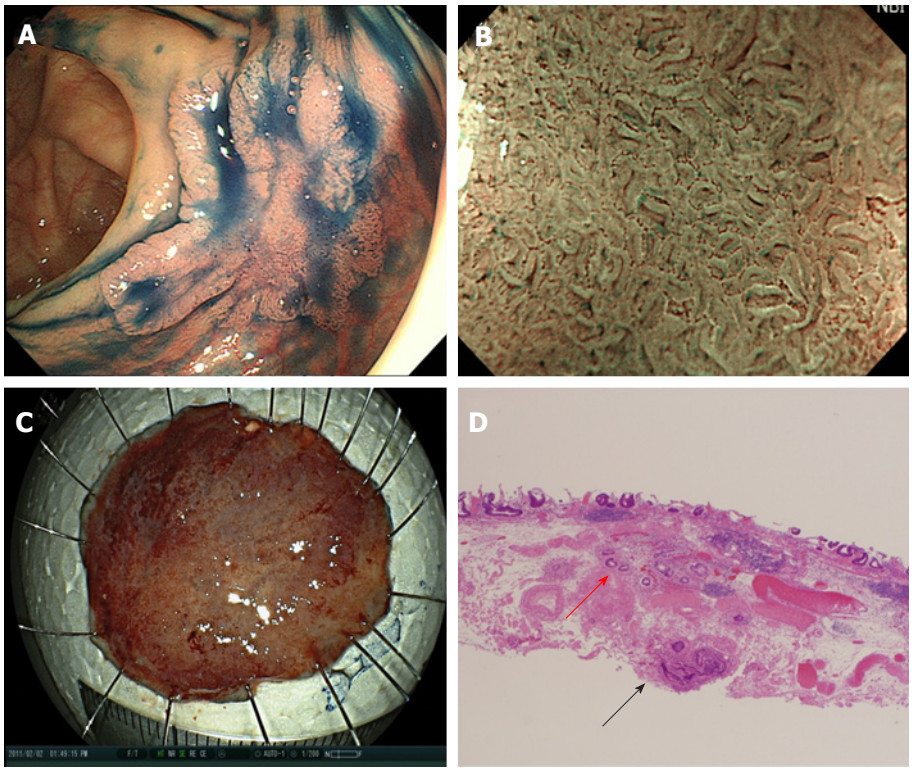

Figure 4 A submucosally invasive cancer with venous infiltration. A: A tumor graded 0-IIa, measuring 20 mm, located in the ascending colon. The surface of the tumor was slightly depressed (shown by indigo carmine dye); B: Magnifying endoscopy with NBI revealed Type C1/C2 according to Hiroshima classification[43]. The tumor was diagnosed as shallow submucosally invasive cancer and endoscopic submucosal dissection (ESD) was performed; C: *En bloc* resection was performed. The ESD operation time was 50 min; D: The histopathological diagnosis of the specimen resected by ESD was massive submucosally invasive cancer. The depth of submucosal invasion was 1300 μm and both a positive vertical margin of the tumor (black arrow) and venous infiltration (red arrow) were detected. The appropriate depth of dissection allowed detection of the positive vertical margin and venous infiltration. Additional surgical intervention was performed and no residual tumor or lymph node metastasis was detected. ESD: Endoscopic submucosal dissection; NBI: Narrow band imaging.

of ESD are postoperative perforation and hemorrhage, similar to those of EMR. In particular, the rate of perforation is higher for ESD than for EMR (1.5%-10.4%). Perforation of the colon can cause fatal peritonitis. Most cases of perforation are treated conservatively by endoscopic clipping, without urgent surgical intervention[40,41]. On the other hand, the rates of postoperative hemorrhage are similar for ESD and EMR. When hemorrhage occurs, endoscopic therapy, including endoscopic clipping, is performed and most cases can be managed conservatively without blood transfusion. A safe strategy, suitable knife, adoption of other equipment and animal training are necessary in order to minimize the complications, including perforation, of ESD[42].

IMPORTANCE OF THE HISTOPATHOLOGICAL EVALUATION OF SUBMUCOSALLY INVASIVE CANCER IN ESD SPECIMENS

Submucosally invasive cancer can be resected by colorectal ESD. A multicenter study of 1111 colorectal ESDs showed that 213 submucosally invasive cancers (19.1%, 213/1111) were treated clinically by ESD[7]. The rate of submucosally invasive cancer in our institution is 10.2% (42/410), which is similar to the rates reported in other studies on colorectal ESD (range: 9.2%-25.0%)[35-37,39]. Moreover, the proportion of massive submucosally invasive cancers in these studies was reported to be 30.0%-58.3%[35-37,39]. Massive submucosal invasion is not in fact an indication for colorectal ESD and EMR; however, endoscopic diagnosis of massive submucosally invasive cancer is limited even when magnifying endoscopy for pit pattern, narrow band imaging (NBI) and flexible spectral imaging color of enhancement (FICE) are performed. The sensitivity of detail-magnifying observation for massive submucosally invasive cancer is only 63.8%-84.8%[32,43-46]. Therefore, some number of massive submucosally invasive cancers may be diagnosed as mucosal cancer or shallow submucosally invasive cancer and scheduled for resection by ESD or EMR (Figure 4). The probability of curative resection of submucosally invasive cancer by ESD is influenced by various clinical features, including histopathological vertical margin, lateral margin and venous-lymphatic invasion. The characteristics of the submucosally invasive cancers treated at our institution are as shown (Table 4). The average tumor size was 26.5 mm in the SM (submucosally invasive cancer) group and 35.1 mm in the M group ($P < 0.01$). The ratio of the number of tumors in the colon to that in the rectum was 18:15 in the SM group, 87:57 in the M (intramucosal

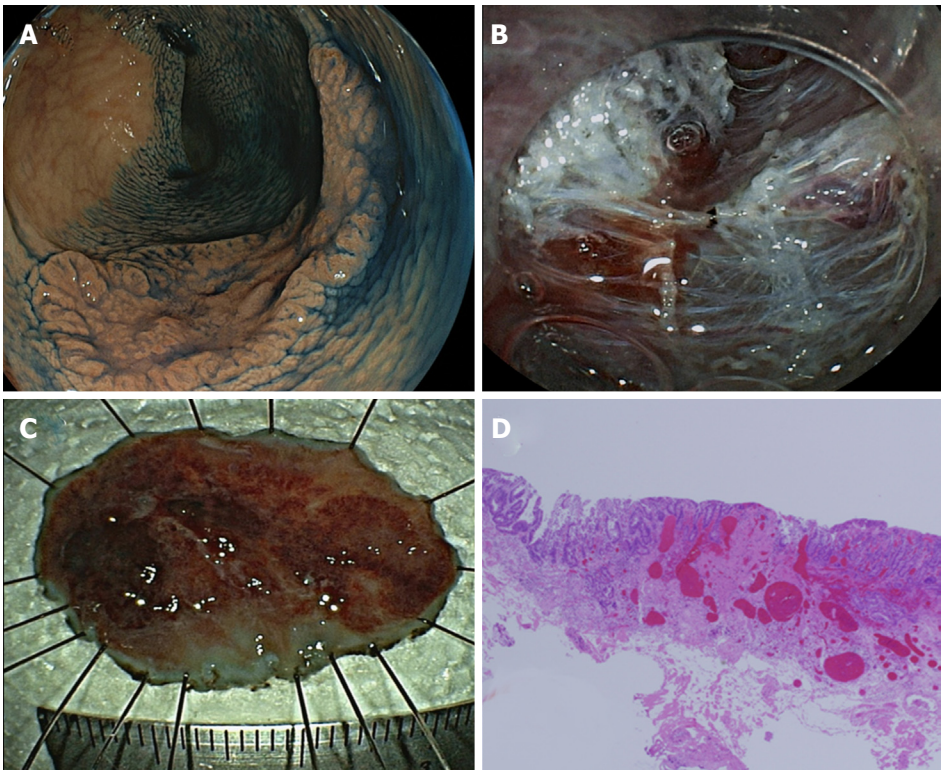

Figure 5 A submucosally invasive cancer with severe fibrosis. A: A tumor graded 0-IIa, measuring 35 mm, located in the descending colon. The surface of the tumor was slightly depressed. The tumor was diagnosed by magnifying endoscopy as shallow submucosally invasive cancer and endoscopic submucosal dissection (ESD) was performed; B: Severe fibrosis was detected during ESD and was dissected with a scissor-type knife; C: *En bloc* resection was performed. The ESD operation time was 160 min. There was no perforation or postoperative hemorrhage; D: Histopathological diagnosis of the specimen resected by ESD was shallow submucosally invasive cancer. The depth of submucosal invasion was 800 μm, and there was severe fibrosis in the submucosa. ESD: Endoscopic submucosal dissection.

Table 4 Characteristics of colorectal tumors resected by endoscopic submucosal dissection

	SM	M	A	*P* value
Number of tumors	33	144	157	
Median age (yr) (range)	65.5 (46-83)	67.9 (48-87)	67.5 (39-87)	
Male/female	21/12	86/58	81/76	NS
Tumor size (mm) (range)	26.5 (10-60)	35.1 (10-130)	27.0 (10-80)	$P < 0.01$
Location (colon/ rectum)	18:15	87:57	124:33	$P < 0.01$ SM:A
Morphology (protruding/ superficial)	14:19	32:112	12:145	$P < 0.01$
Operation time (min) (range)	109 (20-240)	118 (30-420)	92 (10-300)	NS
Severe Fibrosis (%)	18.1	5.5	6.3	$P < 0.05$ SM:M
En bloc resection (%)	90.9	90.9	89.1	NS
Complete resection (%)	72.7	84	81.5	NS
Perforation (%)	6	7.6	1.9	NS
Postoperative hemorrhage (%)	0	6.2	1.2	NS

ESD: Endoscopic submucosal dissection; SM: Submucosally invasive cancer; M: Intramucosal cancer; A: Adenoma; NS: Not significant.

cancer) group and 124:33 in the A group. The proportion of tumors in the rectum was higher in the SM group than in the A (adenoma) group ($P < 0.01$). The ratio of protruding tumors to superficial tumors was significantly higher in the SM group (14:19) than in the M group (32:112) or the A group (12:145) ($P < 0.01$). The rate of severe fibrosis was higher in the SM group (18.1%) than in the M group (5.5%) ($P < 0.05$) (Figure 5). One cause of severe fibrosis is tumor invasion. However, mucosal cancers (5.5%) and adenomas (6.0%) also showed severe fibrosis in our study. Endoscopic biopsy sometimes leads to severe fibrosis. Matsumoto *et al*[47] showed that severe fibrosis complicated ESD and was associated with perforation. The median operation time for the 7 cases in the SM group with severe fibrosis was 147 min, which was longer than that for those in the M group or the A group. Severe fibrosis is difficult to dissect and it should be cautioned that perforation may occur during dissection of severe fibrosis. In our institution, a scissor-shaped knife called the "clutch cutter" (Fujifilm Medical Co., Tokyo, Japan) is used to dissect severe fibrosis with minimal risk of perforation, as it can grasp, coagulate and cut a piece of tissue without perioperative hemorrhage[48].

Among the submucosally invasive cancers, the average depth of submucosal invasion was 449 μm (range: 120-950 μm) in the SM1 group and 5728 μm (range: 1100-8000 μm) in the SM2-3 group. In total, 7 cases of venous invasion (21.2%) and 6 of lymphatic invasion (18.1%) were detected in the SM1 and SM2-3 groups (Table 5). In detail, the rates of venous invasion were 7.6% in the SM1 group and 30.0% in the SM2-3 group, and the rates of lymphatic invasion were 15.3% in the SM1 group

Table 5 Characteristics of submucosally invasive cancer resected by endoscopic submucosal dissection

	SM1	SM2-3	*P* value
Number of tumors	13	20	
Tumor size (mm) (range)	30.7 (20-60)	23.7 (10-60)	NS
Location (colon/ rectum)	8:5	10:10	NS
Morphology (Ⅰs, Ⅰsp/ Ⅱa, Ⅱc, Ⅱa + Ⅱc)	4:9	10:10	NS
Operation time (min) (range)	121 (50-240)	98 (20-230)	NS
Severe fibrosis (%)	15.3	20	NS
En bloc resection (%)	90.9	89.1	NS
Venous invasion (%)	1 (7.6)	6 (30.0)	NS
Lymphatic invasion (%)	2 (15.3)	4 (20.0)	NS
Positive of horizontal margin (%)	3 (23.0)	3 (15.0)	NS
Positive of vertical margin (%)	1 (7.6)	4 (20.0)	NS
Perforation (%)	7.6	1.9	NS

SM: Submucosally invasive cancer.

and 20.0% in the SM2-3 group. Even in shallow submucosally invasive cancers, it was necessary to dissect to the appropriate submucosal depth for the precise detection of venous and lymphatic invasion (Figure 5). If the depth of dissection was too shallow, some cases of venous and lymphatic invasion could not be detected; moreover, the vertical margin could not be evaluated (Figure 6). Therefore, the depth of dissection of colorectal ESD should be carefully considered.

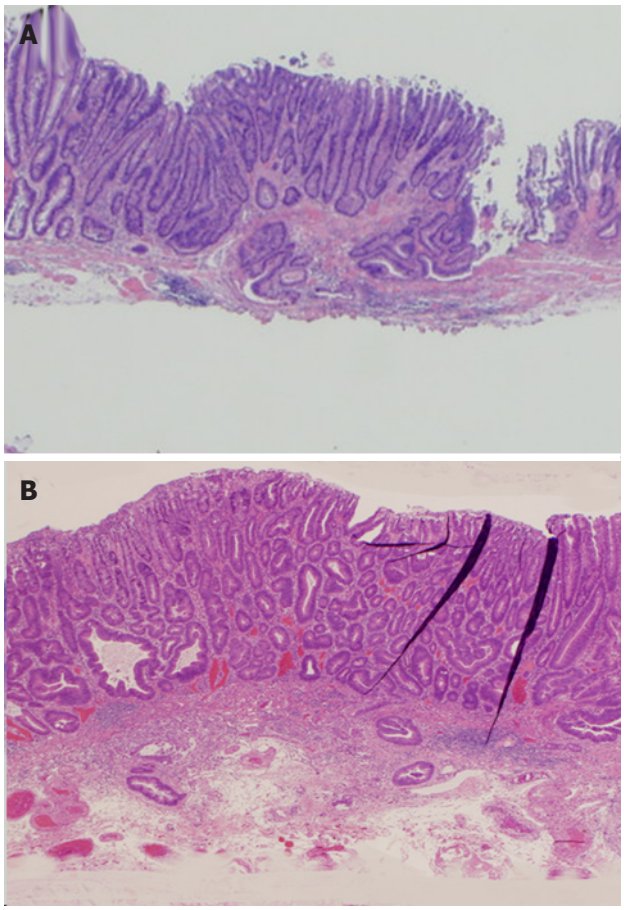

Figure 6 The depth of submucosal dissection in resection of submucosally invasive cancer by endoscopic submucosal dissection. A: The dissection in this case was too shallow. Insufficient submucosa is seen in the resected specimen, which was dissected at the submucosa slightly below the muscularis mucosae. Submucosal invasion can be detected; however, the presence of venous-lymphatic invasion cannot be evaluated; B: This case was dissected appropriately. An adequate amount of submucosa is seen in the resected specimen, which was dissected at the middle-deep submucosa sufficiently below the muscularis mucosae. Both submucosal invasion and venous-lymphatic invasion can be detected.

CONCLUSION

In this review, we describe the different diagnostic criteria for colonic epithelial tumors used around the world. In brief, intramucosal adenocarcinoma is recognized in Japan, while in Western countries adenocarcinoma is diagnosed only if the tumor invades the submucosa and accesses the muscularis mucosae.

Endoscopic treatment, including EMR and ESD, is performed for adenomas and early colorectal cancers worldwide. Precise histopathological evaluation is important for the long-term success of these therapies. Inappropriate endoscopic therapy can lead to local recurrence of the tumor, which sometimes progresses to fatal metastasis. Submucosally invasive cancer is sometimes treated by ESD or EMR. In these cases, very precise histopathological evaluation should be performed in order to determine the necessity of additional therapy, including surgical resection.

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